## Proposed EC/sub-subclass

2.7.11.24

## Accepted name

Mitogen-activated protein kinase 8 (MAPK8)

## Synonyms

c-Jun N-terminal kinase 1 (JNK1); stress-activated protein kinase 1 (SAPK1); JNK1α/β; jnk1a and jnk1b (zebrafish paralogs)

## Phylogeny

JNK1 is one branch of the stress-activated MAPK subfamily that arose early in eukaryotic evolution and is conserved from invertebrates to mammals (Caffrey et al., 2008; Messoussi et al., 2016). Mammals express three closely related isoforms (JNK1-3). JNK1 is ubiquitous, whereas JNK3 is largely restricted to brain, heart and testes (Chrystal, 2015). Orthologs occur in human, mouse, rat and zebrafish; the zebrafish paralogs jnk1a and jnk1b retain high sequence identity with human JNK1 (Chrystal, 2015; Santos-Ledo et al., 2020).

## Reaction catalyzed

ATP + [L-serine/threonine]-protein ⇌ ADP + [L-serine/threonine]-phosphate + H⁺ (Latham et al., 2022).

## Cofactor requirements

Requires divalent Mg²⁺ for optimal ATP binding and catalysis (Latham et al., 2022).

## Substrate specificity

Proline-directed Ser/Thr kinase that prefers a Ser/Thr-Pro motif. Substrates include AP-1 family transcription factors (c-Jun, ATF2, JDP2) and other proteins carrying docking motifs that engage the JNK “D-site” outside the catalytic cleft, thereby enhancing selectivity (Chrystal, 2015; Latham et al., 2022).

## Structure

The protein consists solely of the canonical protein-kinase fold: a β-sheet-rich N-lobe, an α-helical C-lobe and an intervening hinge that forms the ATP pocket (Wu et al., 2018). Key features include  
• Activation loop bearing the dual-phosphorylation TPY motif essential for activity (Latham et al., 2022).  
• A defined docking (D-) site that mediates contacts with upstream kinases and substrates (Wu et al., 2018).  
Crystal and modelling studies highlight conformational plasticity of the ATP site and activation segment that influences inhibitor binding (Caffrey et al., 2008; Messoussi et al., 2016; Wu et al., 2018).

## Regulation

Activation requires dual phosphorylation of Thr-Pro-Tyr by MAP2K4 (MKK4) and MAP2K7 (MKK7) (Latham et al., 2022; Wu et al., 2018). Scaffold proteins (e.g., JIP1, SH3BP5) assemble JNK with its activators and substrates, modulating localization and specificity (Latham et al., 2022; Gehi et al., 2022). Additional regulation arises from further phosphorylation, ubiquitination and other post-translational modifications that alter activity, interactions and stability (Kragelj et al., 2021; Latham et al., 2022; Messoussi et al., 2016).

## Function

JNK1 transduces extracellular stress cues to nuclear responses and governs proliferation, differentiation, migration and apoptosis. Principal substrates are AP-1 transcription factors, whose phosphorylation alters gene programmes linked to inflammation, cell-cycle control and cell death (Chrystal, 2015; Latham et al., 2022). Other reported targets include CDT1 (replication licensing), STMN2 (cytoskeleton) and CLOCK-BMAL1 (circadian clock) (Latham et al., 2022; Wu et al., 2018). Activity contributes to stress-induced p53 and YAP1 phosphorylation, T-cell differentiation and erythroid cell survival (Chrystal, 2015; Gehi et al., 2022; Latham et al., 2022).

## Inhibitors

Both ATP-competitive and substrate/interaction-competitive inhibitors have been developed. Peptide or small-molecule agents that disrupt the JIP–JNK interface provide selectivity by avoiding the highly conserved ATP pocket (Latham et al., 2022; Wu et al., 2018). Structure-guided campaigns have yielded compounds that differentially inhibit JNK1 versus JNK2/3 (Lu et al., 2023; Messoussi et al., 2016).

## Other Comments

Dysregulated JNK1 signalling is implicated in cancer, diabetes, neurodegeneration and inflammatory diseases, driving efforts to design modulators targeting protein–protein interactions within JNK complexes (Latham et al., 2022).

## References

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